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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,120	06/14/2001	David Thomas Dudley	5968-01-SMH	5646

7590

11/26/2003

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EXAMINER
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HUI, SAN MING R

ART UNIT	PAPER NUMBER
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1617

DATE MAILED: 11/26/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

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## Office Action Summary

Application No.

09/868,120

Applicant(s)

DUDLEY ET AL.

Examiner

San-ming Hui

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 22 September 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-19 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All   b) ☐ Some \*   c) ☐ None of:
- 1) ☐ Certified copies of the priority documents have been received.
  - 2) ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - 3) ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

### Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 22, 2003 has been entered.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Mynott et al. (WO 96/00082 provided in the International Search Report).

Mynott et al. teaches bromelain, a MEK inhibitor, is useful in a method of treating rheumatoid arthritis (See page 7, line 17- page 8, line 25; also, page 11, line 21-27; and claims 14-15).

### ***Response to argument with regard to rejection under 35 USC 102(b)***

Applicant's rebuttal arguments averring Mynott's failure to teach bromelain as MEK inhibitor have been considered, but are not found persuasive.

Examiner notes that in the instant specification, the term "MEK inhibitor" is defined as "compounds which inhibit one or more of the family of mammalian enzymes known as MAP kinases, which phosphorylate the MAP kinase subfamily of enzymes (mitogen-associated protein kinase enzymes) referred to as MAP kinase or ERKs. Mynott clearly teaches that bromelain is an agent that can block tyrosine phosphorylation including MAP kinase (also referred as MEK in the instant application, See page 1, line 5 in the Field of the Invention Section) (See Mynott, page 11, line 21- page 12, line 2, particularly page 11, line 24 - 30). Mynott further recites that bromelain is useful as treatment for rheumatoid arthritis (See particularly claim 14). In view of such teaching, the claims are properly rejected under 35 USC 102(b).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyazawa et al. (The Journal of Biological Chemistry, 1998; 273(38): 24832-24838 from the International Search Report), Jackson et al. (The Journal of Pharmacology and Experimental Therapeutics, 1998; 284(2): 687-692 from the International Search Report), Henry et al. (Bioorganic & Medicinal Chemistry Letters, 1998; 8(23): 3335-3340 from the International Search Report), and McGilvray et al. (The Journal of Biological Chemistry, 1997; 272(15): 10287-10294) in view of Bridges (WO 98/37881 from the International Search Report).

Miyazawa et al. teaches that MEK is critically involved in interleukin-6 synthesis by Human fibroblast-like synoviocytes (FLSs), which exhibit inflammatory cells characteristic (See page 24832, col. 1, the abstract and the first paragraph). Miyazawa et al. also teaches that MEK inhibitor can block the activation of MEK and suppression the interleukin-6 production and TNF- $\alpha$  (See page 24837, col. 1, first paragraph and col. 2, second paragraph). Miyazawa et al. also teaches antagonizing interleukin-6 and TNF would be effective in treating rheumatoid arthritis (See particularly page 24837, col. 1, second paragraph). Miyazawa et al also suggests that the inhibitors of MEK would be beneficial as rheumatoid therapy (See particularly page 24837, col. 2, last paragraph).

Jackson et al. teaches inhibition of MEK by a specific MEK inhibitor, SB220025, reducing both interleukin-1 $\beta$  and TNF expression and SB220025 being useful in method of treating chronic inflammation (See the abstract, also page 687; both columns; also page 690, col. 2, second paragraph; particularly page 691, col. 2, last paragraph).

Henry et al. teaches that pro-inflammatory cytokines such as TNF- $\alpha$  and interleukin-1- $\beta$  play important role in inflammatory diseases such as rheumatoid arthritis (See particularly page 3335, first paragraph). Henry et al. also teaches that inhibition of MEK can inhibit TNF- $\alpha$  release and thereby beneficial to rheumatoid arthritis treatment (See page 3335, first paragraph and page 3339, last paragraph).

McGilvray et al. teaches the involvement of MAP kinase (MEK) pathway in the activation of monocytic cells during transmigration to inflammatory sites (See the abstract). McGilvray et al. teaches the selective inhibition of MAP kinase by MEK-1 inhibitor, PD98059, being useful for blocking and interrupting the adhesion and recruitments of human monocytes and thereby modulating the inflammatory response (See the abstract and page 10287, col. 2, second paragraph).

The primary references do not expressly teach the active compounds herein to be MEK inhibitors useful for the treatment of arthritis.

Bridges teaches that the active compounds herein are MEK inhibitors (See page 3, line 16 – page 22, line 29). Bridges also teaches the specific MEK inhibitor recited in claim 17 herein as a preferred MEK inhibitor (See page 22, line 24-25).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the MEK inhibitors of Bridges to treat arthritis such as osteoarthritis and rheumatoid arthritis.

One of ordinary skill in the art would have been motivated to employ the MEK inhibitors of Bridges to treat arthritis such as osteoarthritis and rheumatoid arthritis: the activation of MEK is known to be involved in inflammatory process, such as migration

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and recruitments of monocytes to the inflammatory sites, in the body. Furthermore, the inhibition of MEK is known to 1) suppress the expression and release of pro-inflammatory cytokines such as interleukin-1 $\beta$ , TNF- $\alpha$ , and interleukin-6; and 2) block and interrupt the adhesion of monocytes to the inflammatory sites. Possessing the teachings of the prior art the skilled artisan would therefore employ any known MEK inhibitors, including those MEK inhibitors of Bridges, to treat arthritis such as rheumatoid arthritis and osteoarthritis, absent evidence to the contrary.

### ***Response to Arguments***

Applicant's rebuttal arguments filed September 22, 2003 averring the cited prior art's failure to teach the herein claimed MEK inhibitor have been considered, but are not found persuasive. Applicant specifically remarks on the differences between p38 MAP kinase inhibitors and that of the instant compounds. Examiner notes that the instant claims do not exclude any specific kind of MAP inhibitors. Therefore, such arguments that are drawn to unclaimed limitations is moot. MEK inhibitors, as disclosed in the instant specification page 1, line 5, encompass every types of MAP kinase inhibitors. Therefore, p38 MAP kinase is considered by one of ordinary skill in the art as MEK inhibitors. The broadest claim herein does not distinguish p38 MAP kinase inhibitors from broadly claimed MEK inhibitors as recited herein.

Applicant's rebuttal arguments averring McGilvary alone, in combination with Bridges not providing the motivation to employ MEK inhibitors in the treatment of rheumatoid arthritis have been considered, but are not found persuasive. The rejection

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is based on the combination of Miyazawa et al., Jackson et al., Henry et al., McGilvray et al., and Bridges. Based on the cited prior art, the inhibition of MEK is known to 1) suppress the expression and release of pro-inflammatory cytokines such as interleukin-1 $\beta$ , TNF- $\alpha$ , and interleukin-6; and 2) block and interrupt the adhesion of monocytes to the inflammatory sites. Therefore, possessing the teachings of the cited prior art, one of ordinary skill in the art would employ any known MEK inhibitors, including those MEK inhibitors of Bridges, to treat arthritis such as rheumatoid arthritis and osteoarthritis, absent evidence to the contrary. No such evidence is seen to be present.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.



San-ming Hui  
Patent Examiner  
Art Unit 1617